PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 100848.0204P	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/31556	International filing date *(day/month/year)* 02 October 2002 (02.10.2002)	Priority date *(day/month/year)* 17 January 2002 (17.01.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07H 19/00; A01N 43/04; A61K 31/70 and US Cl.: 536/26.1, 26.11, 26.12, 26.13, 27.21, 27.6, 27.62, 27.6, 27.62, 28.5; 514/43, 45, 46, 47, 48, 49		
Applicant RIBAPHARM INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01 August 2003 (01.08.2003)	03 September 2004 (03.09.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Patrick T. Lewis Telephone No. 571-272-0655

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/31556

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-28 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages NONE, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages 29-33, filed with the demand
pages NONE, filed with the letter of _____.

☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-25	YES
	Claims NONE	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-25	NO
Industrial Applicability (IA)	Claims 1-25	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-25 lack an inventive step under PCT Article 33(3) as being obvious over WO 01/90121 A2 (NOVIRIO PHARMACEUTICALS LIMITED). WO 01/90121 teaches compounds, methods, and compositions for the treatment of hepatitis C in humans or other host animals, that includes administering an effective HCV treatment amount of a β-D- or β-L-nucleoside or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier. The compounds either possess antiviral activity, or are metabolized to a compound that exhibits such activity. The compounds of Formula II as taught by WO 01/90121 embraces the instantly claimed compounds.

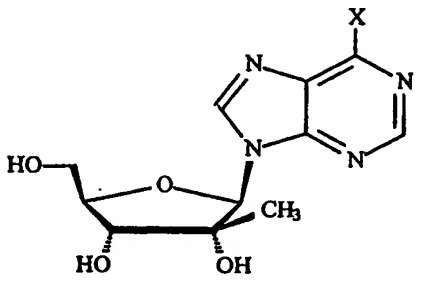
Claims 1-25 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------

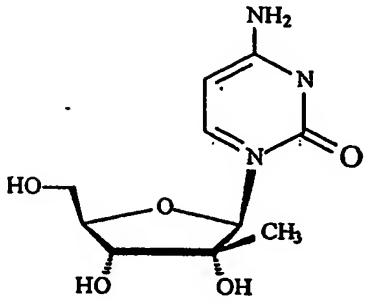
CLAIMS

What is claimed is:

1. A compound according to Formula 1 or Formula 2:



Formula 1



Formula 2

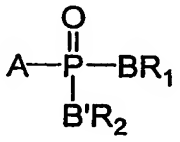
wherein X is selected from the group consisting of NH_2, $NHCH_3$, $N(CH_3)_2$, OCH_3, and SCH_3; and

wherein the compound exhibits an antiviral effect against an HCV virus.

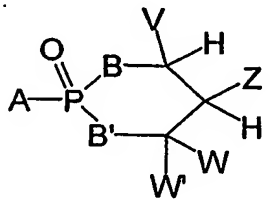
2. The compound of claim 1 further comprising a moiety covalently coupled to at least one of the C2'-atom, C3'-atom, and C5'-atom, and wherein at least part of the moiety is preferentially cleaved from the compound in a target cell or target organ.

3. The compound of claim 2 wherein the moiety comprises a cyclic phosphate, a cyclic phosphonate or a cyclic phosphoamidate.

4. The compound of claim 2 wherein the moiety has a structure according to Formula M1 or Formula M2



M1



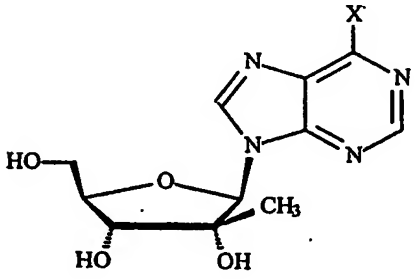
M2

wherein A in M1 or M2 is O or CH_2 and replaces the 5'-OH group of the compound of Formula 1 or Formula 2;

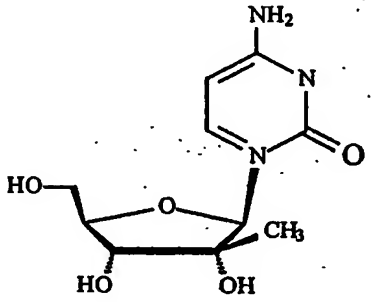
B and B' are independently O or NH, and where B is NH then R_1 or R2 is an amino acid that forms a peptide bond with the N atom of the NH; and

V, W, and W' are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkaryl, each of which is optionally substituted, and Z is hydrogen, CHWOH, CHWOCOW', SW, or CH_2aryl.

5. A pharmaceutical composition comprising a compound of Formula 1 or Formula 2:



Formula 1



Formula 2

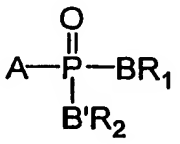
wherein X is selected from the group consisting of NH_2, $NHCH_3$, $N(CH_3)_2$, OCH_3, and SCH_3; and

wherein the compound of Formula 1 or Formula 2 is present in the composition at a concentration effective to inhibit viral RNA replication of an HCV virus.

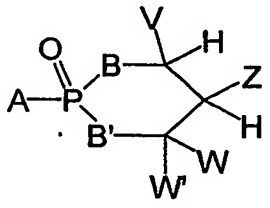
6. The composition of claim 5 wherein the compound further comprises a moiety covalently coupled to at least one of the C2'-atom, C3'-atom, and C5'-atom, and wherein at least part of the moiety is preferentially cleaved from the compound in a target cell or target organ.

7. The composition of claim 6 wherein the moiety comprises a cyclic phosphate, a cyclic phosphonate or a cyclic phosphoamidate.

8. The composition of claim 6 wherein the moiety has a structure according to Formula M1 or Formula M2



M1



M2

wherein A in M1 or M2 is O or CH_2 and replaces the 5'-OH group of the compound of Formula 1 or Formula 2;

AMENDED SHEET

B and B' are independently O or NH, and where B is NH then R_1 or R2 is an amino acid that forms a peptide bond with the N atom of the NH; and

V, W, and W' are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkaryl, each of which is optionally substituted, and Z is hydrogen, CHWOH, CHWOCOW', SW, or CH_2aryl.

9. The composition of claim 5 wherein X comprises a nitrogen atom.

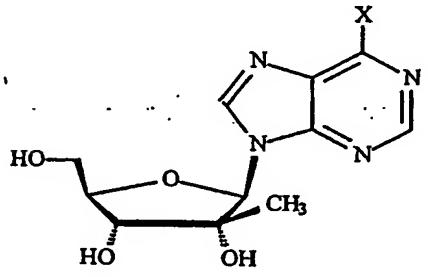
10. The composition of claim 5 wherein X is OCH_3 or SCH_3.

11. Canceled.

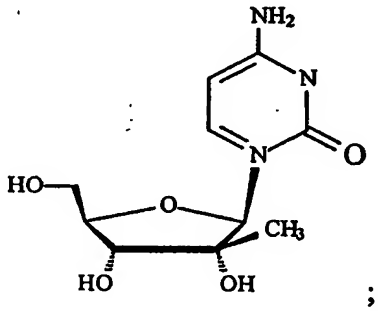
12. The composition of claim 5 wherein HCV replication is mediated by an RNA-dependent RNA polymerase.

13. A method of treating a viral infection in a mammal comprising:

presenting a compound according to Formula 1 or Formula 2 to a cell of the mammal infected with an HCV virus at a concentration effective to reduce viral propagation;



Formula 1



Formula 2

; and

wherein X is selected from the group consisting of NH_2, $NHCH_3$, $N(CH_3)_2$, OCH_3, and SCH_3.

14. The method of claim 13 wherein the viral infection comprises an organ inflammation.

15. The method of claim 13 wherein the cell is a hepatocyte.

16. Canceled.

17. Canceled.

AMENDED SHEET

18. The method of claim 13 wherein the step of presenting comprises intracellular presentation.

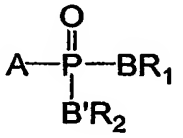
19. The method of claim 13 further comprising administering the compound as a prodrug to the mammal, wherein the prodrug is converted to the compound in the mammal.

20. The method of claim 19 wherein the prodrug is preferentially converted to the compound in the liver.

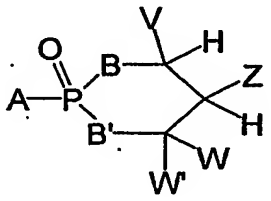
21. The method of claim 19 wherein the prodrug comprises an ester bond that is cleaved to yield the compound.

22. The method of claim 21 wherein the prodrug comprises a cyclic phosphate, a cyclic phosphonate or a cyclic phosphoamidate.

23. The method of claim 21 wherein the prodrug comprises a moiety having a structure according to Formula M1 or Formula M2



M1



M2

wherein A in M1 or M2 is O or CH_2 and replaces the 5'-OH group of the compound of Formula 1 or Formula 2;

B and B' are independently O or NH, and where B is NH then R_1 or R2 is an amino acid that forms a peptide bond with the N atom of the NH; and

V, W, and W' are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkaryl, each of which is optionally substituted, and Z is hydrogen, CHWOH, CHWOCOW', SW, or CH_2aryl.

24. The method of claim 13 further comprising, administration of a second pharmacological molecule.

25. The method of claim 24 wherein the second pharmacological molecule is selected from the group consisting of ribavirin, interferon-alpha, interferon-gamma, and a

AMENDED SHEET

molecule that induces expression of a interferon-alpha or interferon-gamma in the mammal.